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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,199	06/09/2005	Guido Bold	ON/4-32798A	1806

1095 7590 10/18/2007

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CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
ROBINSON, BINTA M	
ART UNIT	**PAPER NUMBER**
1625	

MAIL DATE	DELIVERY MODE
10/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,199	BOLD ET AL.	
	Examiner	Art Unit	
	Binta M. Robinson	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 17-31 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 17-31 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 5/17/06.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 26-32 have been renumbered 25-31.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 25-31 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11-12 of copending Application No. 11374720 (US PG Pub 20060178409). Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application teaches a method of treating retinopathy or age-

related macula degeneration which are neoplastic diseases, with a genus of compounds which overlap is scope with the instant method of treating retinopathy or age-related macula degeneration or treating the human or animal body or the treatment of a neoplastic disease, or the treatment of a neoplastic disease which responds to an inhibition of the VEGF-receptor tyrosine kinase activity.

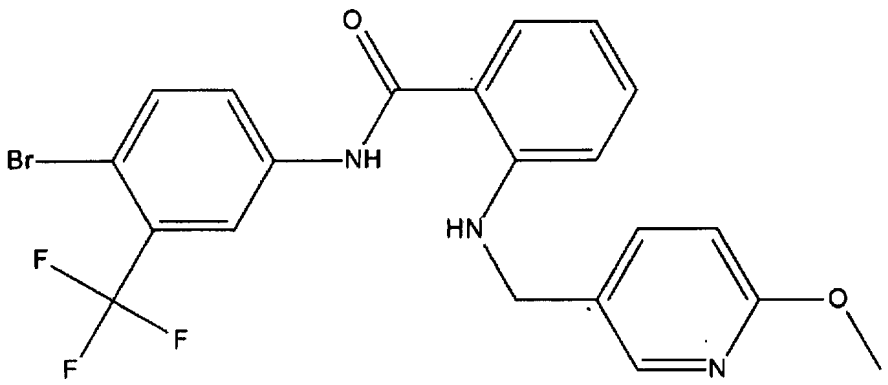
Copending application 11374720 teaches the method for the treatment of retinopathy or age-related macula degeneration, of a neoplastic disease which responds to an inhibition of the VEGF-receptor tyrosine kinase activity with a compound of formula I wherein R1 represents H or lower alkyl, R2 represents H, R3 represents perfluoro lower alkyl, X is O or S. The difference between the copending method and the instantly claimed method is the teaching of a method which overlaps in subject matter with the instant method. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds for the same and/or similar uses. Accordingly, the methods of treating are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed methods over those of the generic copending methods.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

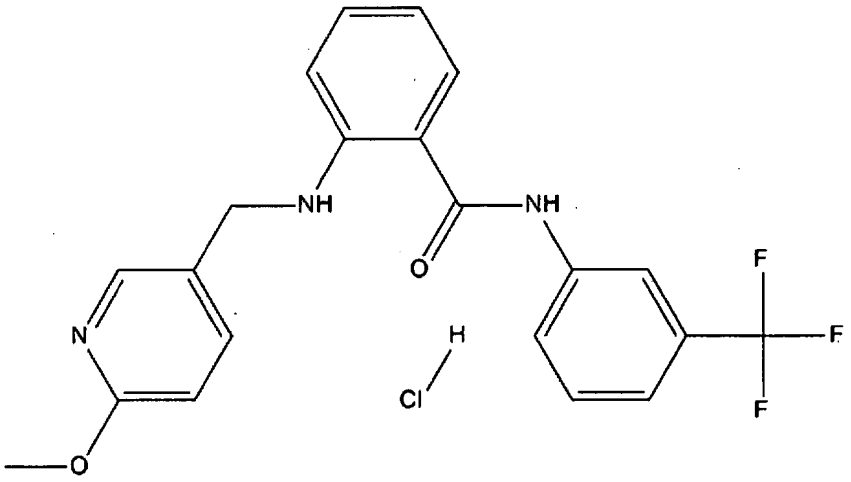
Claims 17, 19, 20, 21, 22, 23, 26-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Bold et. al. Bold et. al. discloses for example, the instant

compound,



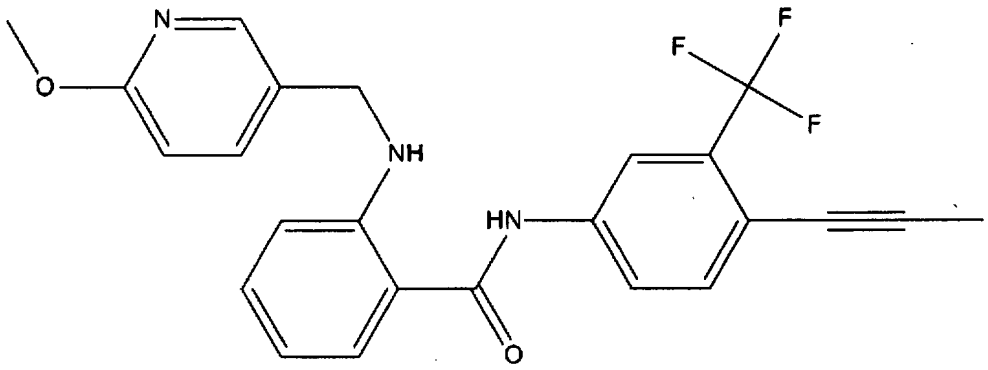
2-[[6-methoxy-3-pyridinyl]methyl]amino-N-[4-bromo-3-(trifluoro-methyl)phenyl]benzamide

at lines 4-5, page 20 and



2-[[6-methoxy-3-pyridinyl]methyl]amino-N-[3-(trifluoromethyl)phenyl]benzamide hydrochloride salt

at page 11, line 27, and



2-[[6-methoxy-3-pyridinyl]methyl]amino-n-[4-(1-propynyl)-3-(trifluoromethyl)-phenyl]benzamide at page 22, lines 16-17.

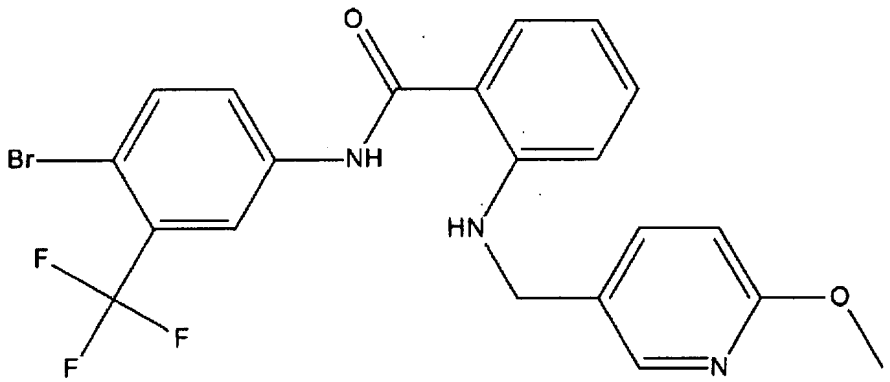
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 17, 19, 20, 21, 22, 23, 26-31 are rejected under 35 U.S.C. 102(e) as being anticipated by Bold et. al.

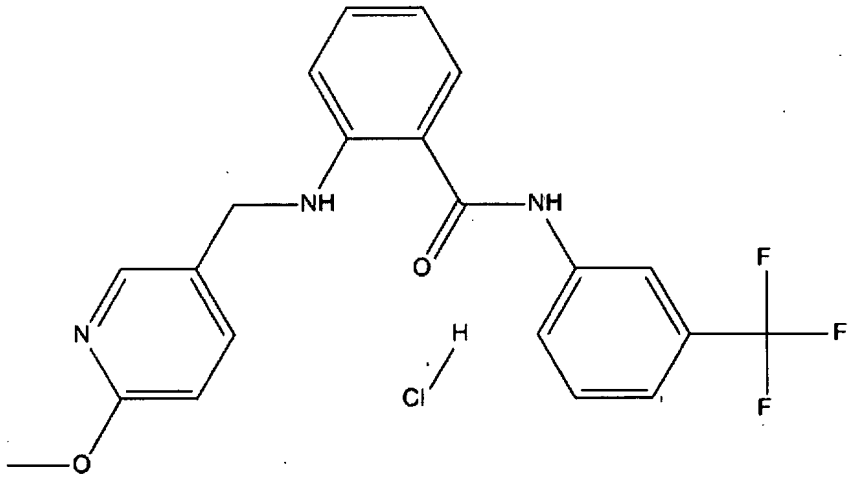
The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Bold et. al. discloses for example, the instant compound,



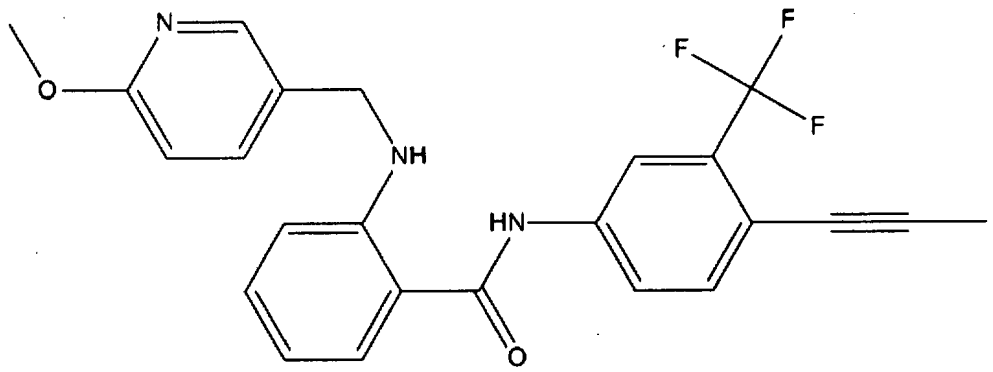
2-[[6-methoxy-3-pyridinyl]methyl]amino-N-[4-bromo-3-(trifluoro-methyl)phenyl]benzamide

at lines 4-5, page 20 and



2-[[6-methoxy-3-pyridinyl]methyl]amino-N-[3-(trifluoromethyl)phenyl]benzamide hydrochloride salt

at page 11, line 27, and



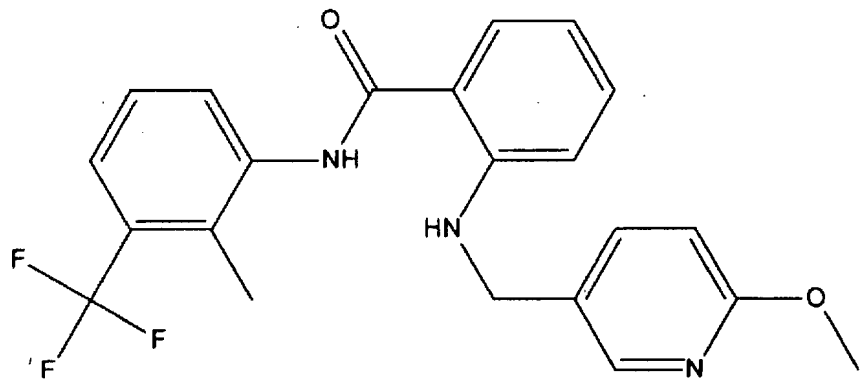
2-[[6-methoxy-3-pyridinyl]methyl]amino-n-[4-(1-propynyl)-3-(trifluoromethyl)-phenyl]benzamide at page 22, lines 16-17.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 17, 19, 20, 21, 22, 23, 26-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bold et. al. (See Reference N).

Bold et. al. teaches the compound,



2-[[6-methoxy-3-pyridinyl]methyl]amino-N-[2-methyl-3-(trifluoromethyl)phenyl]benzamide . At page 11, line 29, see this compound. The difference between the prior art compound and the instantly claimed compounds is the teaching of is the R0 group which is methyl. In the instant application R0 is at the meta position of the phenyl ring. In the prior art compound, the R0 moeity is at the ortho position. The prior art compound is a positional isomer of the instant compound. The prior art compound has pharmaceutical utility. See page 11, lines 1-2. Therefore, It would have been obvious to one of ordinary skill in the art to modify the prior art compound to synthesize the instant compound. Accordingly, the compounds are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the generic prior art compounds.

Claims 17-21, 26, 27, 28, 29, and 30 are rejected under 103 (a) as being unpatentable over Manley et. al. (See Reference O).

Manley et. al. teaches the compound as shown in Formula I, wherein n is 1, W is O, R1 is hydrogen, R2 is an aryl group which group is unsubstituted or mono-or

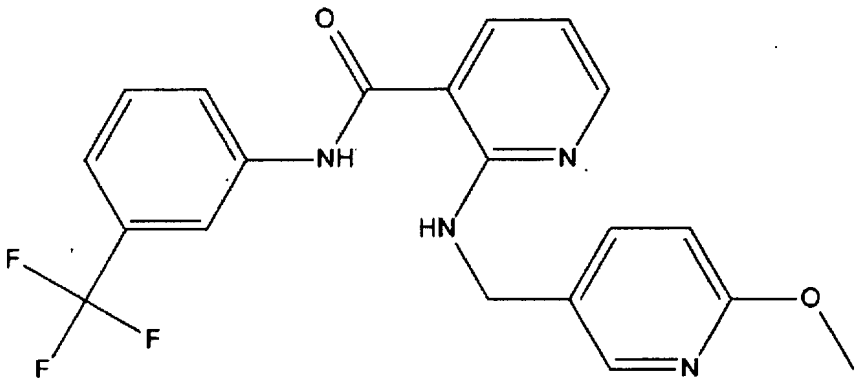
polysubstituted, R and R' are independently of each other hydrogen, X represents a mono-heteroaryl group comproising one nitrogen atom, which group in each case are unsubstituted or mono- or polysubstituted, as well as pharmaceutical compositions containing these compounds, and a method for the treatment of a disease which responds to an inhibition of the VEGF-receptor tyrosine kinase activity with these comounds. See the compound of claim 1 at page 48 as well as the method of use of claim 7 at page 51. The difference between the prior art compound, compositions, and method of use and the instantly claimed compounds, compositions, and method of use is the teaching of a genus which overlaps in subject matter with the genus of the instant application. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds. Accordingly, the compounds, compositions, and method of use are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds, compositions, and methods of use over those of the generic prior art compounds, compositions, and methods of use.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim(s) 17-21, 26, 27, 28, 29, and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Manley et. al. (See Reference O). Manley et. al. discloses for

example, the instant compound,



2-[(6-methoxy-3-pyridyl)methyl]amino-N-[3-(trifluoromethyl)phenyl]-3-pyridinecarboxamide . At page 54, line 3 , see the instant compound.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-24, 25-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using and making the compounds of formula I with Z equal to CH, does not reasonably provide enablement for using the compounds of formula I with Z equal to N. The specification does not enable any skilled pharmacologist or physician to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized above.

a) Determining if any particular claimed compounds of formula I with Z equal to N would be active would require synthesis of the substrate and subjecting

it to testing with Applicants' in vitro enzyme assay, in vivo efficacy assay, and sandwich ELISA assay. Considering the large number of compounds to be made this is a large quantity of experimentation. b) The direction concerning the claimed compounds is found at pages 34-59, which merely states Applicants' intent to make and use such compounds. c) In the instant case, none of the working examples contains radical Z equal to N. d) The nature of the invention is inhibition of VEGF receptor tyrosine kinase and treatment of human diseases with Applicants' compounds. This involves physiological activity. The nature of the invention requires an understanding of the VEGF receptor, the binding activity of small ligands to that receptor, and the ability of those compounds to inhibit this receptor. In view of the unpredictability of receptor binding activity and claimed divergent substituents with varied polarity, size, and polarisability, the skilled physician would indeed question the inclusion of such diverse rings, commensurate in scope with these claims. Also see the MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

e) There is no reasonable basis for the assumption that the myriad of compounds embraced the present formula (I) will all share the same biological properties. The diverse claimed compounds are chemically non-equivalent and

there is no basis in the prior art for assuming in the non-predictable art of pharmacology that structurally dissimilar compounds will have such activity, *In re Surrey* 151 USPQ 724 (compounds actually tested which demonstrated the asserted psychomotor stimulatory and anti-convulsant properties were those having the 3,4-dichlorophenyl substituent at the 2-position on the thiazolidone nucleus not sufficient for enablement of any heterocyclic radical at the same position). *In re Fouche*, 169 USPQ 429 at 434 (a Markush group including both aliphatic and heterocyclic members not enabled for the use of those compounds within the claim having heterocyclic moieties.) *In re CAVALLITO AND GRAY*, 127 USPQ 202 (claims covering several hundred thousand possible compounds, of which only thirty are specifically identified in appellants' application, not enabled unless all of the thirty specific compounds disclosed had equal hypotensive potency because that fact would strongly indicate that the potency was derived solely from the basic structural formula common to all of them. A wide variation in such potency would suggest that it was due in part to the added substituents and might be eliminated or even reversed by many of the possible substituents which had not been tried.)

f) The artisan using Applicants' invention to treat diseases with the claimed compounds would be a physician with a MD degree and several years of experience. He would be unaware of how to predict *a priori* how a changing a

heterocyclic ring would affect biological activity. In view of the divergent rings with varied basicity, steric hindrance, and polarisability, the skilled physician would indeed question the inclusion of such fused rings, commensurate in scope with these claims. g) Physiological activity, is well-known to be unpredictable, *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). h) The breadth of the claims includes all of millions of compounds of formula (I). Thus, the scope is very broad. The present claims embrace various heterocyclic radicals, which are not art-recognized as equivalent. The specific compounds made are not adequately representative of the compounds embraced by the extensive Markush groups instantly claimed. MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly

justified here. Thus, undue experimentation will be required to practice Applicants' invention.

Claim 30 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making solvates and hydrates of the claimed compounds. The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in that art, g) the predictability or unpredictability of the art, h) and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. In the present case the important factors leading to a conclusion of undue experimentation are the absence of any working example of a formed solvate, the lack of predictability in the art, and the broad scope of the claims.

c) There is no working example of any hydrate or solvate formed. The claims are drawn to solvates, yet the numerous examples presented all failed to

produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

g) The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). West, Anthony R., "Solid State Chemistry and its Applications, Wiley, New York, 1988, pages 358 & 365. The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent". Thus, in the absence of

experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate.

h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula I as well as the presently unknown list of solvents embraced by the term "solvate". Thus, the scope is broad.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to practice Applicants' invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 27-28 provide for the use of the compounds of formula I, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 27-28 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating age-related macula degeneration, does not reasonably provide enablement for all treatments of the human or animal body, for diabetic retinopathy, or for the treatment of all neoplastic diseases, or

neoplastic diseases which responds to an inhibition of the VEGF-receptor tyrosine kinase activity. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. The main issues are the correlation between clinical efficacy for treatment of neoplastic diseases which responds to an inhibition of the VEGF-receptor tyrosine kinase activity and Applicants' in vitro enzyme assay, in vivo efficacy assay, and sandwich ELISA assay.

a) Determining if any particular claimed compound would treat any particular neoplastic diseases which responds to an inhibition of the VEGF-receptor tyrosine kinase activity would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a

number of fundamentally different diseases, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large quantity of experimentation. b) The direction concerning treating the claimed diseases is found at page 13, lines 1-13 which merely states Applicants' intention to do so. Applicants describe formulations at page 62. Doses required to practice their invention are described at page 28, line 14-28. A ten-fold range of doses is recommended. Since no one has ever been used to treat any human disease, how is the skilled physician to know what dose to use for each of these different diseases? There are no guidelines for determining the doses needed to provide a VEGF inhibitory effect. Are the identical doses to be used for treating these unrelated diseases? There is a sandwich ELISA assay, a VEGF-induced KDR inhibition assay, and an in vitro enzyme assay described at page 11 with no data but it is unclear if this assay is correlated to treatment of the claimed diseases. c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of neoplastic diseases which responds to inhibition of the VEGF-receptor tyrosine kinase activity with the claimed compound of formula I which involves physiological activity. e) The state of the clinical arts is that in 2002, there was no drug treatment for diabetic retinopathy. See Hcaplus 138:284872.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). h) The scope of the claims involves all of the thousands of compounds of claim 17 as well as the hundred of diseases embraced by the phrase "treatment of the human or animal body" or the phrase "neoplastic

disease" or the phrase "neoplastic disease which responds to an inhibition of the VEGF-receptor tyrosine kinase activity". Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Regarding claim 31, the phrase "if necessary" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Janet Andres can be reached on 571-272-0867.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)-272-1600.

BMR
October 11, 2007

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER